A RING domain-containing protein acts as a repressor of malaria sexual stage conversion

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Molecular Parasitology Meeting 2014, Woods Hole, MA

To become transmissible to mosquitoes, a subset of asexual malaria parasites replicating in human erythrocytes must first transform into a non-replicating sexual stage called the gametocyte. It is hypothesized that asexual parasites become committed to producing offspring that will either begin sexual development or continue asexual replication in the next round. Recent studies have shown that the transcription factor AP2-G is critical for initiating *Plasmodium* gametocyte development and is epigenetically silenced in asexually developing cells. The upstream mechanisms that impose and release this repression are of great interest because of the importance of gametocyte production in malaria transmission.

To identify components of this gametocyte conversion pathway, we performed a genetic screen of a transposon-mutagenized library constructed in the strain NF54. We identified two mutant lines with significantly increased gametocyte conversion rates, suggesting that the disrupted genes are negative regulators of the conversion pathway. One of our mutants has a disruption in a putative E3 ubiquitin ligase (PF3D7_1330500). In addition to increased gametocyte production (4-5 fold compared to the parent), the mutant displays impaired asexual growth and a progressive delay in the cell cycle. This combination of phenotypes was also observed in the recently described disruptions of *P. falciparum* heterochromatic protein 1 (PfHP1) and histone deacetylase 2 (PfHda2); both genes were shown to regulate the activation of AP2-G. Transcriptional analysis of a series of gametocyte markers suggests that the gene acts at or before the point of AP2-G activation. We hypothesize that the protein acts as a repressor of sexual conversion, and we are currently investigating its E3 ligase activity and interaction partners to determine its function.